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Oral Bacteria and Women's Health

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Abstract: This review aims to explore the relationship between oral pathogens associated with periodontitis and diseases and conditions specifically experienced by women. The scientific literature was searched via PubMed between February and June 2024 using the following terms: oral pathogens AND: periodontitis; gingivitis; pregnancy; endometriosis; bacterial vaginosis; breast cancer; ovarian cancer; cervical cancer.

Several oral pathogens, in particular *Fusobacterium* spp., were found to be associated with several women's health issues including pregnancy complications, endometriosis and adenomyosis, bacterial vaginosis and breast, cervical and ovarian cancer. *Fusobacterium* spp, in particular *F. nucleatum*, are significantly more prevalent in the oral cavity of women than men. The demonstration of an association of oral pathogens with a range of women's health conditions poses serious implications for diagnostics, therapeutics, and prevention strategies for these conditions. This is an area that demands further research.

Keywords: oral pathogens, women's health, periodontitis, *F. nucleatum, P. gingivalis.*

1. Introduction

The human body is home to a variety of colonising and pathogenic microorganisms that live in and on organs, tissues and body surfaces. They form microbiomes and these are being increasingly implicated in a range of health and disease conditions. The gut microbiome is the body's largest and most well-studied microbiome. The oral microbiome is the second largest and most diverse microbiome after the gut, with an estimated 700 or more species of colonising bacteria [1]. The sites of colonisation include biofilms on the gums and teeth. It is now well recognised that the oral microbiome plays significant roles in both oral and systemic health [2]. Some pathogenic oral bacteria have been implicated in a range of systemic diseases, including cardiovascular diseases [12], diabetes [13], psoriasis [14], some cancers including head and neck [15], oesophageal [16] and pancreatic cancer [17], and Alzheimer's disease [18].

The Centers for Disease Control and Prevention estimate that almost 70% of Americans 65 and older have some form of gum disease, known as periodontal disease [3]. Periodontal disease is the major cause of tooth loss in adults. Postmenopausal women have a significantly greater risk of periodontitis than non-menopausal women [4].

Periodontal disease can be divided into two sub-conditions – gingivitis and periodontitis. Gingivitis is characterised by inflammation limited to the gingiva. Symptoms are typically red, swollen gums accompanied by mild bleeding. However, if untreated, progressive gingivitis can lead to periodontitis, a more severe form of periodontal disease involving the irreversible destruction of connective tissue and bone, ultimately leading to tooth loss [5]. Bacteria are the primary cause of periodontal diseases.

Absuleme et al. [6], analysed the oral microbiomes in gingivitis and periodontitis and compared them to healthy, or disease-free, oral microbiomes. The researchers determined that the changes in the subgingival microbiome in people with periodontitis were "dramatically different from" those in gingivitis sufferers, which were in turn significantly different from healthy people. They postulated that the bacteria that cause symptoms of gingivitis assist the establishment of periodontitis-associated bacteria. "The emergence of periodontitis-associated taxa as low-abundance species in gingivitis is compatible with the concept that certain low-abundance species with specific virulence factors dysregulate host-protective mechanisms and initiate the events that lead to profound dysbiosis and periodontal tissue destruction" [6].

Cluster analysis has shown that the periodontal-associated bacteria can be sorted into five major groups that were given color designations [7]. The designated "red" complex (*Porphyromonas gingivalis, Treponema denticola* and *Bacteroides forsythus*) and the "orange" complex (*Fusobacterium nucleatum* subspecies, *Prevotella intermedia, Prevotella nigrescens, Peptostreptococcus micros, Eubacterium nodatum, Streptococcus constellatus,* and three *Campylobacter* species) were generally found together. Evidence also showed that colonization by the red complex was preceded by colonization by the orange complex species [8].

Sneathia spp. (Gram-negative rods, anaerobic), are also implicated in periodontal disease [9]. They are classified as part of the *Fusobacteria* [10] and are closely related to the *Leptotrichia* genus. This is significant, as 30% of the organisms identified in gingivitis are members of the *Leptotrichia* genus [6]. *Sneathia* spp. have been identified in the oral cavity, gastrointestinal tract, and the cervix and/or vagina. In addition to its association with periodontitis, it has been identified as an important contributor to common obstetric, neonatal and gynecologic pathologies [11].

Some of the periodontal-associated bacteria, in particular *P. gingivalis* and *F. nucleatum*, have been associated with the range of systemic diseases listed above. To date, there have been few reports of an association between pathogenic oral bacteria and diseases or conditions specific to women's health.

2. Associations between women's health and oral health

There is emerging evidence that the presence of oral pathogens associated with periodontal disease is associated with a number of specifically women's health issues, including:

- Pregnancy and its complications;
- Endometriosis and adenomyosis;
- Bacterial vaginosis;
- Female cancers (breast cancer; ovarian cancer; cervical cancer)

Evidence for the association between bacteria found in the oral cavity and these conditions is summarised in Table 1 and presented in more detail below.

Table 1. Oral bacteria associated with systemic women's health disorders

Disease / condition	Oral pathogens	References
Pregnancy complications	*P. gingivalis; F. nucleatum*, *Sneathia* spp.	5, 43-46
Endometriosis	*F. nucleatum*	49,50
Adenomyosis	*L. zeae, P. copri*	51
Bacterial vaginosis	*Sneathia* spp., *F. nucleatum*	57
Breast cancer	*F. nucleatum*	59, 62,63
Ovarian cancer	*Fusobacterium, S. mitis, C. simulans/striatum, D. invisus*	63, 70
Cervical cancer	*Fusobacterium*, *Sneathia* spp., *P. anaerobius*	71,72, 74

2.1. Pregnancy complications

Pregnant women are highly susceptible to periodontal disease [36]. In fact, the prevalence of periodontitis in pregnancy can be as high as 40% [37]. Of concern, there is evidence that maternal periodontal disease is strongly associated with poor pregnancy outcomes, in particular preterm birth, low birth weight, and pre-eclampsia [38-40]. The likelihood of a woman with periodontal disease experiencing preterm birth was estimated to be 5-38%; 6-41% for low birth-weight, and 10-55% for pre-eclampsia [41]. Oral pathogens that have been identified to be associated with pregnancy complications include: *P. gingivalis* [43]; *F. nucleatum* [44]; *Prevotella melaninogenica* [5,45], and *Sneathia spp*. [46]. Dental treatment during pregnancy appears unlikely to reduce the risk of these adverse pregnancy outcomes [42], therefore it seems prudent to provide a preventative therapy for women planning to become pregnant.

2.2. Endometriosis and Adenomyosis

2.2.1 Endometriosis

Endometriosis is a chronic, painful disease that is characterised by endometrial-like tissue growing outside the uterus, and affects around 10-15% of women of child-bearing age worldwide [47]. This extra-uterine growth leads to systemic inflammation, chronic pelvic pain, and heavy bleeding during or between menstruation. The cause of endometriosis is not well understood. Retrograde menstruation has been proposed as a potential cause; however, it appears that most women experience retrograde menstruation whilst only 10-15% develop endometriosis [48].

Multiple bacterial genera have been identified in the endometria of women with endometriosis, including *Fusobacterium* and *Porphyromonas*, however, to date, the findings have lacked consistency [49]. However, in 2023 a study implicating *Fusobacterium* infection specifically as a significant contributor to the pathogenesis of endometriosis was published [50]. Using quantitative PCR (qPCR) analysis of tissue samples obtained from 79 patients, the results showed that *Fusobacterium* infiltration, mostly *F. nucleatum*, was significantly more frequent in endometrial tissues from patients with endometriosis compared with the controls ($p<0{\cdot}01$). Furthermore, *Fusobacterium* infection of endometrial cells

activated TGFβ expression, a cytokine known to play a major role in endometriosis. In *in vivo* experiments inoculation of tissue from *F. nucleatum*-infected uteri from donor mice caused the formation of multiple endometriotic lesions in recipient mice. These findings suggest that *Fusobacterium* infection may cause or contribute to the pathogenesis of endometriosis and that antibiotics and antibacterial agents directed to *Fusobacterium* species to eradicate endometrial infection should be investigated.

2.2.2 Adenomyosis.

Adenomyosis differs from endometriosis in that the uterine tissue does not leave the uterus, but instead grows into the muscular wall of the uterus. It presents as chronic pain and heavy bleeding between and during periods. As with endometriosis, the cause is not clear. Lin et al. [51] reported that patients with adenomyosis had significantly elevated levels of five bacterial species compared to the control group without adenomyosis. These were identified as *Lactobacillus zeae, Burkholderia cepacia, Weissella confusa, Prevotella copri,* and *Citrobacter freundii*. It is pertinent to note that two of these (*L. zeae* and *P. copri*) are found in the oral cavity, with *L. zeae* being associated with periodontitis [52,53].

2.3. Bacterial vaginosis

Bacterial vaginosis (BV), a condition characterized by decreased vaginal lactobacilli and increased anaerobic bacteria, has been associated with an increased risk of preterm birth [54], as has periodontal disease as discussed above. Symptoms of vaginal dysbiosis include a malodorous discharge. Some microflora characteristic of BV have strong similarities to periodontal disease-associated bacterial species. As Persson et al. [55] point out, *Prevotella bivia* and *Porphyromonas* spp. have been associated with BV, whereas *Prevotella intermedia* and *Porphyromonas gingivalis* have been associated with periodontal disease. However, there are few studies investigating the direct relationship between oral and vaginal infections. Persson et al. [55] reported significantly ($p < 0.001$) higher vaginal bacterial counts in women with a concurrent diagnosis of gingivitis compared to women who had neither BV nor gingivitis. The authors concluded that *Prevotella bivia* and *Prevotella disiens* may be of specific significance in an association between vaginal and periodontal infections. A more recent study found that *Pseudomonas aeruginosa* and *Prevotella intermedia* were increased in the saliva of women with a vaginal dysbiosis [56]. These authors suggested that the data may indicate a relationship between oral and vaginal dysbiosis, warranting further investigation into whether they are causally related. Ling et al. [57] determined that the bacterial diversity of the BV microbiome was dominated primarily by *A. vaginae*, *Sneathia* spp., and *Fusobacterium nucleatum* subsp., amongst others.

2.4. Female cancers

It is interesting to note that the microbiome in general has been implicated in several aspects of the cancer process, including cell proliferation, creation of inflammatory microenvironments, metastasis, and chemotherapy resistance [58].

2.4.1 Breast cancer

A little recognised fact is that the breast contains a distinct and unique microbiome. Of relevance to this discussion, *Fusobacterium nucleatum* has been identified as a key member [59], and several studies have confirmed that the breast microbiome is altered in breast tumours compared with healthy tissue [60,61]. For example, the expression of *F. nucleatum* DNA was reported to be significantly higher in breast cancer tissue than in control, non-cancerous breast tissue and positively associated with tumor size and metastasis [59,62]. The researchers who identified this shift in *F. nucleatum* expression postulated that *F. nucleatum* modulates two well-defined hallmarks of cancer, notably immune escape and inflammation within the tissue microenvironment. Furthermore, the microbiome, and *F. nucleatum* specifically, has been shown to adversely affect patient response to therapy including immune checkpoint inhibitors. *Fusobacterium* was also one of five oral bacterial genera identified as promoting breast cancer in an Asian population [63].

Whilst interesting, there is no evidence that the *F. nucleatum* associated with breast cancer originates from the oral cavity. However, there are some epidemiological findings that suggest that periodontal diseases may be associated with breast cancer [64], indicating that this may be possible. Söder et al. [65] reported that women suffering from periodontal disease were more than twice as likely to be diagnosed with breast cancer compared to healthy women. Furthermore, using missing molars as a surrogate for severity of periodontitis, the researchers reported that severity of periodontitis appears to correlate with the risk of developing breast cancer. Of the subjects with periodontal disease and missing molars, 5.5% had breast cancer in comparison to 0.5% of the subjects who had periodontal disease but no missing molars. They concluded from this analysis that "… chronic periodontal disease indicated by missing molars seemed to associate statistically with breast cancer" [65].

Given this, how could *F. nucleatum* travel from the oral cavity to the breast? Guo et al. [66] attempted to address this question. They proposed that *F. nucleatum* can enter mammary tissue via three routes: "direct nipple contact, the mammary-gut axis, and hematogenous transmission". Subsequently, they hypothesise, *F. nucleatum* colonizes breast cancer cells and uses virulence factors (fusobacterium adhesin A and LPS) to promote proliferation, and matrix metalloproteinase-9 to trigger the inflammatory response and facilitate the tumor-promoting microenvironment. Interestingly, in considering the likelihood of the nipple route of colonization, *F. nucleatum* is the most common microorganism found

in the mouth of breast-feeding newborns [67]. Arguing against this route of transmission, however, is the finding that nulliparous women have a 20%–40% higher risk of postmenopausal breast cancer than women who first gave birth before age 25 [68].

2.4.2. Ovarian Cancer

Ovarian cancer (OC) is the 7th most common cancer in the world. According to Globocan's 2020 projections [69], who predict that by 2040, the number of women around the world diagnosed with ovarian cancer will rise almost 42% to 445,721. The number of women dying from ovarian cancer each year is projected to increase to 313,617, an increase of over 50% from 2020. There is some evidence substantiating a causal relationship between oral bacteria and OC. There are at least two relevant recent studies. Firstly, Feng et al. [63] identified *Fusobacterium* as an oral pathogen that promotes ovarian cancer using genomic datasets of multiple cancers and controls focusing on Asian populations. Secondly, in a large prospective study, Yu et al. [70] profiled the microbiota in the Fallopian tube (FT) to assess its relationship with OC. There was a clear shift in the FT microbiome of the OC patients when compared to that of non-cancer patients. Of the top twenty bacterial species that were most prevalent in the FT of OC patients, 30% normally reside in the oral cavity. By contrast, in non-cancer patients, vaginal bacterial species represented 75% of the top 20 most prevalent species.

A recent report by Barnard et al. [71] that women with endometriosis have an overall > 4-fold risk of contracting ovarian cancer in general may further support a bacterial (in particular *F. nucleatum*) cause of this cancer, given the link between F. *nucleatum* and endometriosis discussed above. In fact, the report found that the more severe the endometriosis, the greater the risk (rising to 9.7-fold higher for deep infiltrating endometriosis). The association between endometriosis subtypes and specific ovarian cancer histotypes was much higher for type I (10-19-fold) compared with type II (high-grade serous; 3-fold) ovarian cancers [71].

2.4.3 Cervical Cancer

Persistent infection with subtypes of the human papillomavirus (HPV) is known to be a major cause of cervical carcinogenesis. There is evidence however, that bacterial oral pathogens may also play a role in the cancer process. A 2013 Korean study of identical female twins showed that the vaginal microbiomes of HPV-infected individuals contained much lower levels of the normally dominant *Lactobacillus* spp. and significantly elevated levels of *Fusobacteria* and *Sneathia* spp. than those of their non-infected siblings [72]. Additionally, *Sneathia* spp. and another oral microbe, *Peptostreptococcus anaerobius* were detected in HPV-infected patients with high grade (but not low grade) squamous intra-epithelial lesions [73]. *Sneathia amnii* has been shown to bind to the surface of malignant cervical epithelial cells [11]. This suggests a potential for toxic products released by adherent *Sneathia* to alter the characteristics of host tissue and directly mediate effects on the cervical microenvironment. An analysis of correlations between the severity of cervical neoplasms and vaginal microbiomes found that *Sneathia* spp. were enriched in all precancerous women with cervical epithelial neoplasia but not in patients with invasive cervical carcinoma [74]. Vaginal *Sneathia* may therefore be induced by HPV infection, and play a role in the early stage of cervical carcinogenesis – the onset of cervical intraepithelial neoplasia, and precancerous neoplastic progression. *Fusobacterium* spp. is often found in the female reproductive tract [75]. In cervical cancer, *Fusobacterium* spp. have been identified to be the dominant vaginal microbiome species [76]. *Fusobacterium* spp. has been implicated in the promotion of the development of dysplasia in colorectal cancer [77]. It is possible therefore that in a similar fashion, the vaginal microbiota may be linked to cervical cancer. In a Korean twin cohort study, *Fusobacterium* spp. served as a microbial marker to observe HPV infection. In addition, the cytokine profile showed that the local levels of interleukin-4 (IL-4) and transforming growth factor- β1 (TGF-β1) were significantly increased in the cervix vaginal microflora dominated by *Fusobacterium* spp. in a *Lactobacillus* deficiency. Elevated mRNA levels of TGF-β1, IL-4, and interleukin-10 (IL-10), were also found in cervical biopsies from patients with the squamous intraepithelial disease and cervical cancer [78]. Thus, another cancer promoting mechanism of *Fusobacterium* may be via inducing an immunosuppressive microenvironment characterized by anti-inflammatory cytokines. These studies provide evidence that *Fusobacterium* spp. may play a role in the occurrence and progression of cervical cancer.

3. Discussion and Conclusion

The human oral microbiome is a complex conglomeration of organisms that changes in response to various local and systemic conditions, in a two-way interaction. At various stages in a woman's life such as pregnancy and menopause, the risk of developing periodontal disease, driven by oral pathogens, is significantly increased. The oral microbiome has been historically associated with oral-specific diseases such as gingivitis and periodontitis, but there is now significant emerging evidence indicating its potential influence on a range of systemic conditions.

From Table 1, *Fusobacterium* spp., in particular *F. nucleatum*, is commonly implicated in most of the women's health conditions and diseases. A key member of the orange complex, *F. nucleatum* is a Gram-negative anaerobe which is localised in the oral cavity under normal conditions. Under disease conditions, however, *F. nucleatum* is recognised as one of the most prevalent species found in extra-oral sites [79].

A 2022 review concluded that *F. nucleatum* can induce an immune response and inflammation in the body through direct or indirect pathways, and thus affect the occurrence and development of a range of systemic diseases [80].

Whilst there have been few studies specifically focussing on the link between women's health and the oral microbiome, given that there is a reasonable body of evidence that has demonstrated links between the oral microbiome and several types of cancers, including colorectal cancer, lung cancer, and pancreatic cancer, it seems likely that similar links will be confirmed for cancers of female organs and tissues. Such connections are already starting to be found, as discussed above.

Beyond cancer, it is clear that a link is emerging between the presence of oral pathogens that cause periodontitis and gingivitis and conditions and diseases specifically affecting women. These include endometriosis, bacterial vaginosis and complications of pregnancy. It is pertinent to note that *Fusobacterium* spp, in particular *F. nucleatum*, are significantly more prevalent in the oral cavity of women than men, and even more so in women over 30 years of age [81]. The association of oral pathogens with female-specific conditions poses profound implications for diagnostics, therapeutics and in particular, prevention strategies for a range of women's health conditions.

The emerging understanding of the impact of the oral microbiome on a range of women's health issues should open the consideration of complementary therapies such as the use of prebiotic compounds and probiotic strains for global or targeted modulation of the oral microbiome in order to have a favourable influence on supporting women's health. In addition, this understanding should also have relevance for improved diagnostics. Kamer et al. [82] showed that antibody levels to periodontal bacteria correlate with the presence of Alzheimer's disease and thus could help improve its clinical diagnosis. By extension, monitoring antibody levels to periodontal bacteria could also be an important addition to the diagnosis of a range of female-specific diseases and conditions listed above.

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